Impact of cataract surgery on depression and cognitive function: a systematic review and meta-analysis

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ABSTRACT

Importance: In elderly people, visual impairment is associated with depressive symptoms and cognitive decline. However, the impact of cataract surgery on depression and cognitive impairment is still controversial.

Background: To evaluate the effect of cataract surgery on depression and cognitive status in the elderly.

Design: Meta-analysis.

Participants: Patients with age-related cataract who underwent cataract surgery.

Methods: A literature search was performed on Pubmed, Scopus, and Web of Science. Data were extracted from selected studies by two independent reviewers. The pooled standardized mean difference (SDM) was estimated using a random-effects model. Heterogeneity was evaluated using the Q and I^2 tests. Multiple sensitivity analyses and assessment of publication bias were performed.

Main Outcome Measures: Report of a measure of depression or cognitive impairment before and after surgery.

Results: Sixteen studies were included: 14 of them reported data on depression, and 9 of them on cognitive function. Depression significantly decreased after surgery (SDM=0.460; 95% CI: 0.223–0.697; $P<0.001$). In 6 controlled studies, the reduction of depression was higher in the surgery group than in the control group (SDM=0.161; 95% CI: 0.027–0.295; $P=0.019$). Cognitive function significantly improved after surgery (SDM=0.254; 95% CI: 0.120–0.388; $P<0.001$). In 4 controlled studies, the improvement of cognitive function was higher in the surgery group than in the control group (SDM=0.188; 95% CI: 0.002–0.374; $P=0.048$). Results were stable after sensitivity analyses.

Conclusions and Relevance: This meta-analysis provides evidence that cataract surgery has a positive effect on depression and cognitive function in the elderly.

1. INTRODUCTION

Cataract is a major cause of visual impairment and blindness worldwide.[1] The burden of cataract is predicted to increase dramatically over the next decades, especially in Western countries, because of longer life expectancies and progressive ageing of population.[2]

Adequate vision is an important aspect for physical and cognitive function.[3,4] There is growing body of evidence that visual impairment in the elderly contributes to cognitive decline.[5,6] Moreover, the loss of vision caused by senile cataract has shown a strong association with depressive symptoms.[7-9] In elderly people, depression often coexists with cognitive impairment, worsening the outcome of many medical illnesses and increasing disability and mortality.[10]

Cataract surgery is a highly effective intervention, resulting in almost immediate vision recovery. In addition to visual acuity improvement, strong evidence indicates that cataract surgery significantly ameliorates quality of life.[11,12] Some studies suggested that cataract surgery may also improve cognitive function and reduce depressive and neuropsychiatric symptoms.[13-15] However, other studies reported no significant effects upon these functions.[16-17] To our knowledge, no systematic review on this topic has been published and therefore, the impact of cataract surgery on depression and cognitive impairment is still controversial.

The aim of this systematic review and meta-analysis was to identify, evaluate, and summarize the available evidence to determine if there is an overall significant improvement in depression and cognitive impairment after cataract surgery.

2. METHODS

2.1 Search Strategy

An *a priori* protocol defining eligibility criteria, search strategy, outcomes of interest, and analyses methods was developed. The study was conducted following to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[18] Relevant published studies were identified by searching Pubmed, Scopus, and Web of Science through September 2019. The key words "cataract surgery" OR "cataract extraction" AND "depression" OR "depressive symptoms" OR "cognition" OR "cognitive status" OR "cognitive function" OR "cognitive impairment" OR "mental status" were used. No language restriction was applied. In addition, the bibliographies of relevant articles were reviewed manually to identify additional publications.

2.2 Study Selection

The articles retrieved were considered eligible when they met the following inclusion criteria: (1) prospective design; (2) population: patients with age-related cataract; (3) intervention: cataract surgery; (4): outcome: report of a measure of depression or cognitive impairment before and after surgery; (5): language: English. Conference proceedings and abstracts, letters, reviews, editorials, cross-sectional or case-control studies and full texts without raw data available for retrieval were excluded. Studies focused on specific subsets of patients, such as those with Alzheimer disease, were also excluded.

Duplicate publications were removed after the literature search. Then, the title and abstracts of all identified citations were screened independently by two reviewers. The full-text of articles that potentially matched the inclusion criteria were retrieved and re-screened for eligibility. Disagreements between the two reviewers were resolved by consultation with all authors.

2.3 Data Extraction and Quality Assessment

Two reviewers (MP & FB) independently extracted the following data from each study: (1) study characteristics, including the first author, publication year, journal, country, study design, length of the follow-up, number of patients, demographics, visual acuity before and after surgery; (2) outcome measures (depression or cognitive impairment) before and after surgery. In case of discordant data, the manuscripts were revisited. Missing data were obtained by contacting the study authors.

The methodological quality of each study was assessed using the Methodological Index for Non-Randomized Studies (MINORS) score system. This tool assigns scores ranging from 0 to 24 evaluating 12 criteria: (1) a clearly stated aim; (2) inclusion of consecutive patients; (3) prospective collection of data; (4) endpoints appropriate to the aim of the study; (5) unbiased assessment of the study endpoint; (6) follow-up period appropriate to the aim of the study; (7) loss to follow-up of less than 5%; (8) prospective calculation of the study size; (9) an adequate control group; (10) contemporary groups; (11) baseline equivalence of groups; (12) adequate statistical analysis.[19]

2.4 Data Analysis

To examine the effect of cataract surgery on depression and cognitive function, data were analysed using a random effect model, which considered both within- and between-study variation. The effect size for the change in depression and cognitive function before and after surgery was estimated using the standardized difference in mean values (SDM), which was calculated from sample size, pre-treatment mean and standard deviation (SD), post-treatment mean and SD. For the studies that had a control group, the between-group SDM was also calculated to estimate the difference in effect between the cataract surgery group and the control group. A pre-post correlation coefficient of 0.69 was calculated from one of the included studies, and was used in cases where pre-post correlations where not reported in the original paper.[20] $P < 0.05$ was considered statistically significant.

The Q and I^2 tests were employed to evaluate heterogeneity.[20] Sensitivity analyses were performed first by removing the studies with the highest risk of bias, then by removing one study at a time from the meta-analysis to verify whether the results would change. A subgroup analysis was performed by grouping studies that used the same tool. Potential publication bias was assessed by both visual evaluation of funnel plots and Egger's test.[21]

A meta-regression was performed to evaluate the effect of covariates on the change in depression and cognitive function after surgery, specifically: age, baseline visual acuity, final visual acuity, length of follow-up. All statistical analyses were conducted using the Comprehensive Meta-Analysis software (version 3; Biostat, Inc., US).

3. RESULTS

3.1 Characteristics of Studies

The flow chart of the literature search and study selection is presented in Figure 1. A total of 708 articles were initially identified. Following the screening of titles and abstracts, 42 articles were retrieved for full-text review. Finally, 16 articles that met the inclusion criteria were included in the meta-analysis (Table S1).[22-37]

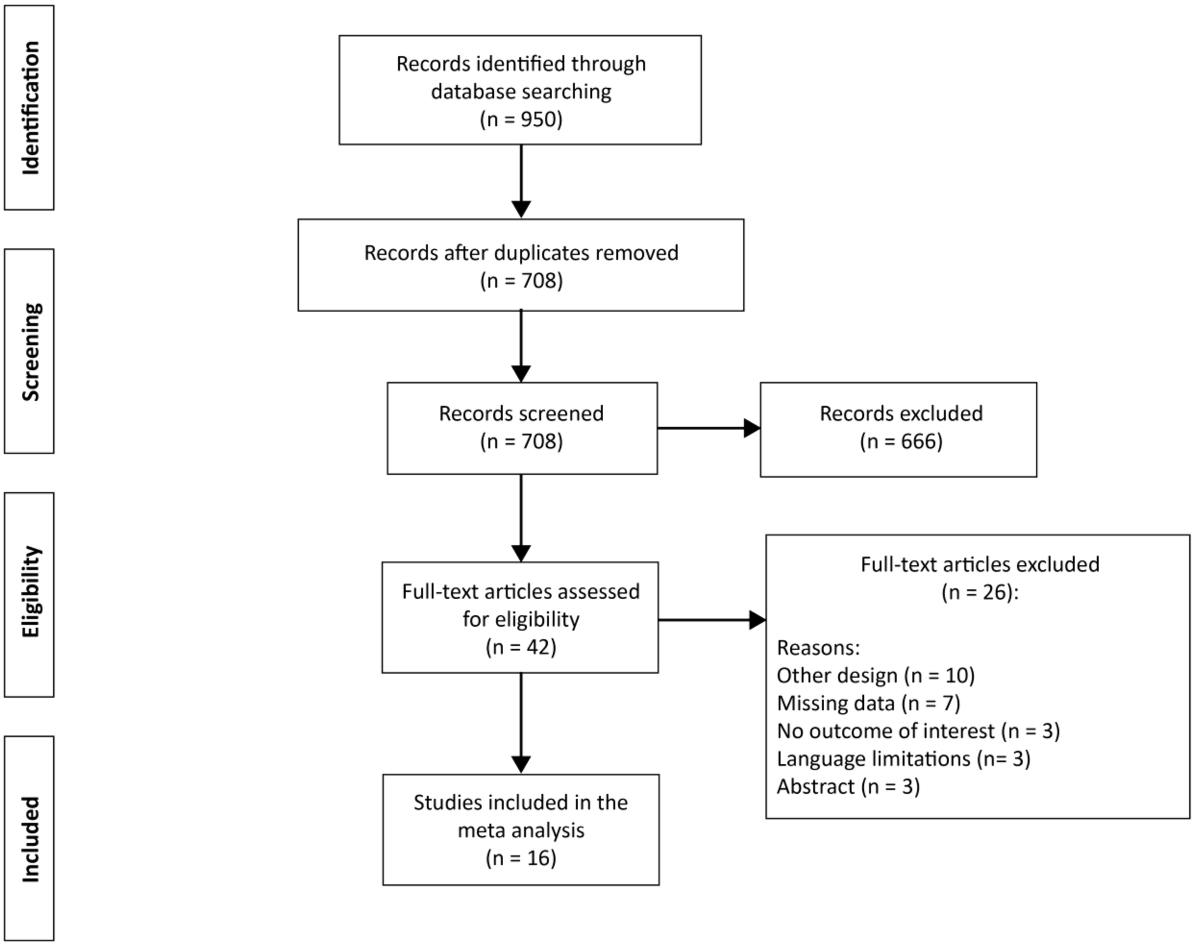

Figure 1: Flow diagram of the study selection process.

The characteristics of the included studies are reported in Table 1. The studies were published between 1996 and 2018, and included a total number of 1308 patients who underwent cataract surgery. Five of them were conducted in the United States of America,[23,24,30,31,34] 2 in China,[29,33] 2 in Japan,[25,35] 2 in Vietnam,[22,36] 1 in the United Kingdom,[26] 1 in Iran,[27] 1 in France,[28] 1 in Greece,[32] and 1 in Australia.[37] The duration of the follow-up ranged from 1 to 12 months. In total, 14 studies reported data on depression. Of these, 5 studies used the Geriatric Depression Scale (GDS),[23,26-28,34] 4 the Center for Epidemiological Studies Depression Scale (CES-D),[24,30,31,36] 1 the Self-Reporting Questionnaire-20 (SRQ-20),[22] 1 the Beck Depression Inventory (BDI),[25] 1 the Hamilton Rating

Scale for Depression (HAM-D),[32] 1 the Self-rating Depression Scale (SDS),[33] and 1 the Depression Anxiety Stress Scale (DASS).[37]

In total, 9 studies reported data on cognitive function. Of these, 5 studies used the Mini-Mental State Examination (MMSE),[23,25,27,29,33] 2 the Mattis Organic Mental Syndrome Screening Examination; (MOMSSE)[24,31], 1 the Addenbrooke's Cognitive Examination (ACE-R),[26] and 1 the Revised Hasegawa Dementia Scale (HDS-R).[35]

Ten studies had a control group.[23,24,29-35,37] Except for one study,[37] none of them had a randomized design. Six of them reported data on depression in both groups,[23,24,30,31,34,37] allowing the calculation of between-group SDM; while 4 of them reported cognitive function data in both groups.[23,24,31,35]

Table 1. Characteristics of the studies included in the meta-analysis.

First author (year)	Country	Control group	Follow-up (months)	Sample size	Mean age	Gender (male%)	Depression tool	Cognitive status tool
Berle et al., 2016 [22]	Vietnam	No	12	381	70.2	36.0%	SRQ-20	-
Billig et al., 1996 [23]	U.S.	Yes	12	91	75.9	31.5	GDS	MMSE
Hall et al., 2005 [24]	U.S.	Yes	12	122	70.9	41.8	CES-D	MOMSSE
Ishii et al., 2008 [25]	Japan	No	2	88	75.3	40.9	BDI	MMSE
Jefferis et al., 2015 [26]	U.K.	No	12	91	80.7	45.0	GDS	ACE-R
Kheirkhah et al., 2018 [27]	Iran	No	3	196	71.8	49.0	GDS	MMSE
Leruez et al., 2015 [28]	France	No†	3	34	76.5	20.6	GDS	-
Lin et al., 2018 [29]	China	Yes	6	26	63.8	50.0%	-	MMSE
McGwin et al., 2003 [30]	U.S	Yes	12	146	70.8	41.8	CES-D	-
McGwin et al., 2006 [31]	U.S.	Yes	12	122	70.9	41.8	CES-D	MOMSSE
Mitsonis et al., 2006 [32]	Greece	Yes	1	121	-	34.7	HAM-D	-
Ni et al., 2015 [33]	China	Yes	4	56	69.1	-	SDS	MMSE
Owsley et al., 2007 [34]	U.S.	Yes	4	30	81.0	26.7	GDS	-
Tamura et al., 2004 [35]	Japan	Yes	1	20	81.8	30.0	-	HDS-R
To et al., 2014 [36]	Vietnam	No‡	3	140	66.5	32.1	CES-D	-
Walker et al., 2006 [37]	Australia	Yes	3	25	73.4	44.4	DASS	-

ACE-R: Addenbrooke's Cognitive Examination; BDI: Beck Depression Inventory; CES-D: Center for Epidemiological Studies Depression Scale; DASS: Depression Anxiety Stress Scale; GDS: Geriatric Depression Scale; HAM-D: Hamilton Rating Scale for Depression; HDS-R: Revised Hasegawa Dementia Scale; MMSE: Mini-Mental State Examination; MOMSSE: Mattis Organic Mental Syndrome Screening Examination; SDS: Self-rating Depression Scale; SRQ-20: Self-Reporting Questionnaire-20. U.K.: United Kingdom. U.S. United States.

† The study separated the participants in two groups based on the type of intraocular lens (untinted vs yellow-tinded IOL). However, data from the total cohort were retrieved for analysis.

‡ The study compared patients who had surgery in the first eye with those who had surgery in both eyes. Data from the group that had surgery in both eyes were retrieved for analysis.

Table 2 reports the risk of bias assessment for each study included in the meta-analysis according to the MINORS score system. The total quality score of studies ranged between 11 and 22 out of a maximum score of 16 for uncontrolled studies and 24 for controlled studies. The most common short-coming was the lack of prospective calculation of the study size, which was performed in only one study.[27] Other common biases were the loss to follow-up greater than 5% and the lack of information on the consecutiveness of patients. For controlled studies, the main bias was the lack of baseline equivalence between the surgery group and the control group.

Table 2. Quality of the studies included in the meta-analysis assessed by the Methodological Index for Non-Randomized Studies (MINORS) score system.

First author (year)	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	Total
Berle et al., 2016 [22]	2	0	2	2	2	2	1	0	-	-	-	-	11
Billig et al., 1996 [23]	2	2	2	2	2	2	1	0	1	2	1	2	19
Hall et al., 2005 [24]	2	2	2	2	2	2	0	0	2	2	1	2	19
Ishii et al., 2008 [25]	2	0	2	2	2	2	1	0	-	-	-	-	11
Jefferis et al., 2015 [26]	2	2	2	2	2	2	1	0	-	-	-	-	13
Kheirkhah et al., 2018 [27]	2	0	2	2	2	2	1	2	-	-	-	-	13
Leruez et al., 2015 [28]	2	2	2	2	2	2	2	0	2	2	2	2	22
Lin et al., 2018 [29]	2	2	2	2	2	2	2	0	2	2	2	2	22
McGwin et al., 2003 [30]	2	2	2	2	2	2	1	0	2	2	1	2	20
McGwin et al., 2006 [31]	2	2	2	2	2	2	1	0	1	2	1	2	19
Mitsonis et al., 2006 [32]	2	0	0	2	2	2	1	0	1	2	2	1	15
Ni et al., 2015 [33]	1	0	0	2	2	2	2	0	1	2	1	2	15
Owsley et al., 2007 [34]	2	0	2	2	2	2	2	0	2	2	2	2	20
Tamura et al., 2004 [35]	2	0	2	2	2	2	2	0	1	2	1	1	17
To et al., 2014 [36]	2	2	2	2	2	2	1	0	-	-	-	-	13
Walker et al., 2006 [37]	2	2	2	2	1	2	1	0	2	2	2	2	20

The MINORS score system evaluates 12 criteria: (1) a clearly stated aim; (2) inclusion of consecutive patients; (3) prospective collection of data; (4) endpoints appropriate to the aim of the study; (5) unbiased assessment of the study endpoint; (6) follow-up period appropriate to the aim of the study; (7) loss to follow-up of less than 5%; (8) prospective calculation of the study size; (9) an adequate control group; (10) contemporary groups; (11) baseline equivalence of groups; (12) adequate statistical analysis. The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate).

3.2 Quantitative Analysis

In the 14 studies reporting the change in depression before and after surgery, the overall SDM was 0.460 (95% CI: 0.223 – 0.697; *P* < 0.001), indicating a significant reduction in depression after surgery (Figure 2).

	SDM	95% CI		*P*-Value
Berle 2006	1.150	1.049	1.252	<0.001
Billig 1996	0.038	-0.123	0.199	0.646
Hall 2005	0.115	-0.024	0.255	0.106
Ishii 2008	0.156	-0.009	0.321	0.063
Jefferis 2015	0.075	-0.086	0.237	0.360
Kheirkhah 2018	0.631	0.520	0.743	<0.001
Leruez 2014	0.440	0.191	0.689	0.001
Mcgwin 2003	0.107	-0.021	0.235	0.100
Mcgwin 2006	0.115	-0.026	0.257	0.110
Mitsonis 2006	0.701	0.545	0.857	<0.001
Ni 2015	2.101	1.733	2.469	<0.001
Owsley 2017	0.180	-0.103	0.463	0.212
To 2014	0.453	0.316	0.589	<0.001
Walker 2006	0.349	0.032	0.666	0.031
	0.460	0.224	0.697	<0.001

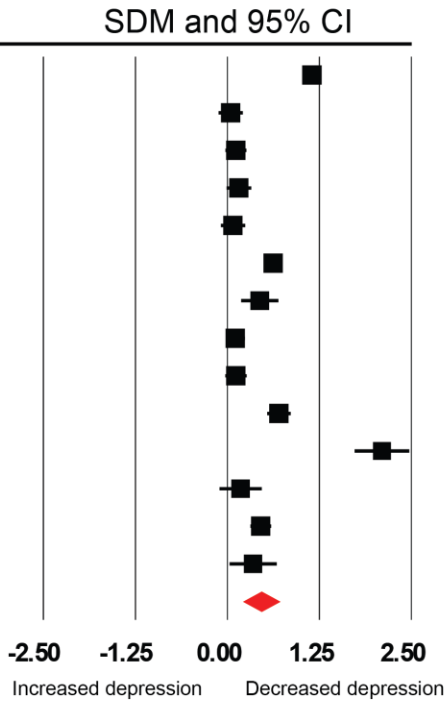

Figure 2: Forest plot of studies that evaluated depression before and after cataract surgery. SDM indicates standardized difference in mean values, which was computed using a random-effect model.

A significant heterogeneity was detected (Q = 413.1, I^2 = 96.9%). After the exclusion of the 4 studies with the highest risk of bias,[22,25,32,33] the SDM was 0.248 (95% CI: 0.097 – 0.399; *P* = 0.001). The exclusion of any single study at a time from the meta-analysis did not significantly alter the pooled estimates, and the SDM ranged from 0.349 (95% CI: 0.127 – 0.572; P = 0.002) to 0.494 (95% CI: 0.247 – 0.740; P < 0.001) (Table S2). No significant publication bias was detected by both visual evaluation of funnel plots and the Egger test (P = 0.688). The subgroup analysis revealed a significant difference in the SDM among studies that used different tools to evaluate depression (P < 0.001) (Table S3). The reduction in depression after surgery remained statistically significant within the subgroup of studies using CES-D (SDM = 0.197; 95% CI: 0.031 – 0.364; P = 0.020) within the subgroup of studies using GDS (SDM = 0.275; 95% CI: -0.007 – 0.558; P = 0.056). Meta-regression found a significant association between the reduction in depression and the baseline visual acuity (B = 0.656; 95% CI: 0.133 – 1.180; P = 0.014). Conversely, no significant association of the depression improvement with mean age of patients (P = 0.059), length of follow-up (P = 0.236) or final visual acuity (P = 0.298) was found.

In the 9 studies reporting the change in cognitive function before and after surgery, the overall SDM was 0.254 (95% CI: 0.120 – 0.388; P < 0.001), indicating a significant improvement of cognitive function after surgery (Figure 3).

	SDM	95% CI		*P*-Value
Billig 1996	0.062	-0.099	0.224	0.450
Hall 2005	0.171	0.031	0.312	0.017
Ishii 2008	0.262	0.095	0.428	0.002
Jefferis 2015	0.150	-0.012	0.312	0.070
Kheirkhah 2018	0.081	-0.029	0.191	0.151
Lin 2018	1.285	0.877	1.692	<0.001
Mcgwin 2006	0.188	0.048	0.329	0.009
Ni 2015	0.099	-0.107	0.305	0.346
Taumra 2004	0.701	0.318	1.085	<0.001
	0.345	0.179	0.512	<0.001

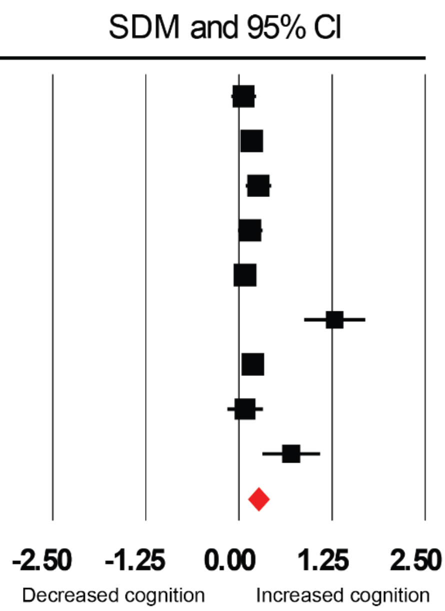

Figure 3: Forest plot of studies that evaluated cognitive function before and after cataract surgery. SDM indicates standardized difference in mean values, which was computed using a random-effect model.

A significant heterogeneity was detected (Q = 42.1; I^2 = 81.0%). After the exclusion of the 3 studies with the highest risk of bias,[25,33,35] the SDM was 0.238 (95% CI: 0.071 – 0.404; *P* = 0.005). The exclusion of any single study at a time from the meta-analysis did not significantly alter the pooled estimates, and the SDM ranged from 0.164 (95% CI: 0.085 – 0.243; *P* < 0.001) to 0.286 (95% CI: 0.135 – 0.436; *P* < 0.001) (Table S4). Egger test was positive (*P* = 0.005), suggesting the possibility of publication bias. The subgroup analysis revealed a significant difference in the SDM among studies that used different tools to evaluate depression (*P* < 0.001) (Table S5). The improvement of cognitive function remained statistically significant within the subgroup of studies using MMSE (SDM: 0.287; 95% CI: 0.052 – 0.522; *P* = 0.017), and within the subgroup using MOMSSE (SDM: 0.180; 95% CI: 0.081 – 0.279; *P* < 0.001). Meta-regression found no significant association of the cognitive improvement with baseline visual acuity (*P* = 0.592), final visual acuity (*P* = 0.638), mean age of patients (*P* = 0.271), length of follow-up (*P* = 0.239).

In the 6 studies reporting the change in depression in both the surgery group and the control group, the between-group SDM was 0.161 (95% CI: 0.027 – 0.295; *P* = 0.019), indicating higher reduction in depression in the surgery group (Figure 4). No between-study heterogeneity was detected (Q = 1.3, I^2 = 0.0%). No significant publication bias was detected by both visual evaluation of funnel plots and the Egger test (*P* = 0.930).

	SDM	95% CI		*P*-Value
Billig 1996	0.021	-0.345	0.386	0.912
Hall 2005	0.165	-0.110	0.441	0.239
Mcgwin 2003	0.194	-0.058	0.446	0.132
Mcgwin 2006	0.165	-0.110	0.441	0.239
Owsley 2017	0.071	-0.549	0.690	0.824
Walker 2006	0.392	-0.201	0.986	0.195
	0.161	0.027	0.295	0.019

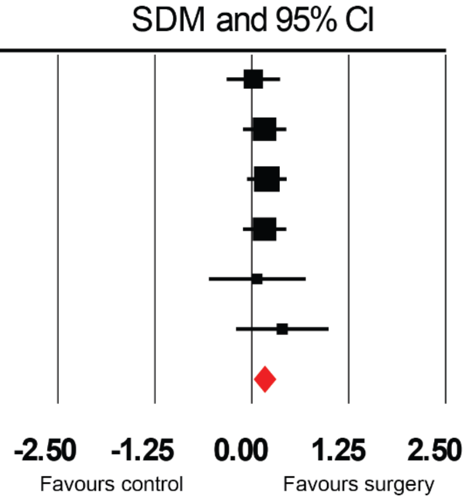

Figure 4: Forest plot of studies that evaluated depression comparing cataract surgery with a control group. SDM indicates standardized difference in mean values, which was computed using a random-effect model.

In the 4 studies reporting the change in cognitive function in both the surgery group and the control group, the between-group SDM was 0.188 (95% CI: 0.002 – 0.374; P = 0.048), indicating higher cognitive improvement in the surgery group (Figure 5). The between-study heterogeneity was low (Q = 3.6, I^2 = 16.1%). No significant publication bias was detected by both visual evaluation of funnel plots and the Egger test (P = 0.081).

	SDM	95% CI		*P*-Value
Billig 1996	0.135	-0.231	0.501	0.471
Hall 2005	0.132	-0.143	0.407	0.347
Mcgwin 2006	0.144	-0.132	0.419	0.307
Tamura 2004	0.779	0.136	1.422	0.018
	0.188	0.002	0.374	0.048

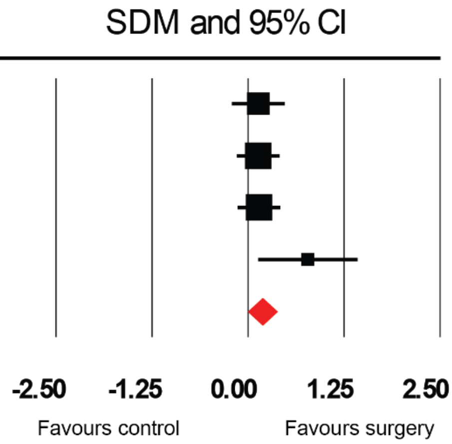

Figure 5: Forest plot of studies that evaluated cognitive function comparing cataract surgery with a control group. SDM indicates standardized difference in mean values, which was computed using a random-effect model.

4. DISCUSSION

In this systematic review, we found sixteen studies evaluating the change in depression or cognitive function after cataract surgery. The results of the meta-analysis indicated that cataract surgery provides benefits with regard to depressive symptoms. This effect was confirmed also in the studies that compared the outcomes between surgery and control groups. The stability of the results after sensitivity analyses and the absence of publication bias support the robustness of these findings. Cognitive function also significantly increased after surgery, with higher improvement in surgery group compared to control group. However, the effect size was lower, and the possibility of publication bias could not be excluded. Therefore, this result should be interpreted with more caution.

Only one of the studies included in this systematic review had a randomized design.[37] In many cases, authors perceived randomization as unethical, because cataract surgery is a standard-of-care treatment that cannot not be denied.[24,25,31,34] In non-randomized studies the control group was composed either by patients with cataract who declined surgery,[24,30,31,34] or by age-matched healthy subjects.[22,29,32,34] However, declining surgery or not suffering from cataract with visual impairment could have a significant interaction on depression and cognitive function, and this may constitute an important bias. Therefore, we decided to include in the meta-analysis also uncontrolled studies, using the change in depression and cognition before and after surgery as an outcome. Since it is unlikely that these parameters would fluctuate significantly in the short term,[38,39] it is reasonable to attribute their change to the effect of cataract surgery.

The results of this meta-analysis were based on studies of moderate quality. All the studies except one did not calculate prospectively the sample size; while some of them were unclear on the consecutiveness of patients and presented a high rate of loss to follow-up. Excluding the studies with the highest risk of bias did not alter significantly the results of the meta-analysis. However, the studies had significant differences regarding the inclusion and exclusion criteria, follow-up duration, demographics and clinical parameters such as visual acuity. All these factors could have contributed to the high between-study heterogeneity. A lower heterogeneity was present in studies with a control group, but the overall effect size was also lower in these studies.

In the meta-regression, we found a significant association between the postoperative improvement in depression and the baseline visual acuity. Previous studies demonstrated that patients awaiting cataract surgery with worse visual acuity are more likely to be depressed.[8,9] Therefore, it is not surprising the improvement in depression after surgery is higher in this subset of patients. We were not able to identify any association between the effects of cataract surgery on depression and cognition and the length of the follow-up. Hence, it is still unknown whether these benefits would be transitory or persist over time in the long term. If they result from the relief of the psychological distress caused by cataract and by anticipation of the surgical procedure,[22] they might gradually decrease over time. However, a recent study found that cataract surgery had a positive impact on trajectories of cognitive decline over 13 years of follow-up.[40] Interestingly, a functional magnetic resonance imaging study demonstrated that cataract surgery can reverse the functional and structural brain changes caused by cataract, with improvement of grey matter volume and fractional amplitude of low-frequency fluctuations in vision and cognition related areas.[29]

This meta-analysis suffers from some limitations. First, it included observational studies, most of which did not have a control group. Therefore, it is difficult to discern the true effect of cataract surgery from other factors related to the procedure, such as the stress of surgery and the expectation to recover, all of which may influence the answers to questionnaires. Although the effect of surgery was confirmed in controlled studies, selection bias could have occurred in the recruitment of control subjects. In addition, the quality of the studies was suboptimal, and they differed in terms of characteristics of the population, duration of the follow-up and tools used to measure depression and cognitive function. The presence of unmeasured confounders and the methodological differences among studies resulted in high heterogeneity, and this limits the generalizability of our results. Finally, publication bias could not be excluded for studies evaluating cognitive function before and after cataract surgery.

In conclusion, our meta-analysis suggests a positive effect of cataract surgery on depression and cognitive function. Although methodological limitations of the available evidence preclude the drawings of definitive conclusions, clinicians should consider cataract surgery as a potentially useful intervention to improve mental and cognitive health in later life.

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